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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/738,917	12/16/2003	Holly Hogrefe	04121.0116-08000	8386

22852 7590 06/02/2006

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EXAMINER	
RAMIREZ, DELIA M	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 06/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/738,917	HOGREFE ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *96-112* is/are pending in the application.

4a) Of the above claim(s) *108 and 109* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *96-107 and 110-112* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 March 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/10/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Claims 96-112 are pending.

It is noted that the examination of the instant application has been assigned to a different Examiner in Group Art Unit 1652.

Applicant's election of Group I, claims 96-107, 110-112 drawn to compositions comprising enzymes, in a communication filed on 3/10/2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 108-109 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Specification

1. Applicant's preliminary amendment of the first paragraph of the specification as submitted on 12/16/2003 is acknowledged. It is noted however that the status of U.S. Application No. 09/399003 and 08/822774 has not been updated. These applications have now issued as patents. Appropriate correction is required.

2. The use of the trademarks has been noted in this application. See, for example, "Perfect Match" on page 68, line 16, "Bluescript" on page 35, line 27. They should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. Applicant's cooperation is requested in reviewing the specification for additional trademarks that may be present in the specification and making the appropriate correction(s).

Priority

3. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 120 or 121 to US application No. 09/399,003 filed on 09/20/1999, 08/957,709 filed on 10/24/1997, 08/822,774 filed on 03/21/1997, and PCT/US98/05497 filed on 03/20/1998.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on 3/10/2006 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Drawings

5. The drawings submitted on 3/24/2005 have been reviewed and are accepted by the examiner.

Claim Objections

6. Claims 99, 103-105 are objected to due to the recitation of "is *Pyrococcus furiosus* dUTPase", "is *Pyrococcus furiosus* DNA polymerase", and "is *Thermus aquaticus* DNA polymerase" as being grammatically incorrect. It is suggested the terms be amended to recite "is a *Pyrococcus furiosus* dUTPase", "is a *Pyrococcus furiosus* DNA polymerase", and "is a *Thermus aquaticus* DNA polymerase". Appropriate correction is required.

7. Claims 96 and 110 are objected to due to the recitation of "(a) an enzyme possessing substantial....., (b) a DNA polymerase wherein the DNA polymerase has less 3' to 5' exonuclease activity than the enzyme, and (c)". While the Examiner has interpreted the term "the enzyme" in part (b) as referring to the enzyme described in part (a), it is noted that there is more than one enzyme recited in the

claim, such as the DNA polymerase of part (b). To avoid any confusion, it is suggested the term be amended to recited "(a) an enzyme possessing ....., (b) a DNA polymerase wherein the DNA polymerase has less 3' to 5' exonuclease activity than the enzyme of (a)", or similar. Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 96-107, 110-112 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claims 96, 107, 110 (claims 97-106, 111-112 dependent thereon) are indefinite in the recitation of "an enzyme possessing substantial 3' to 5' exonuclease activity" and "factor that substantially inhibits the incorporation..." for the following reasons. The terms "substantial" and "substantially" are relative terms which have not been defined in the claims, and the specification provides no standard for ascertaining the requisite degree. Thus, one of skill in the art would not be reasonably apprised of the scope of the claims. For examination purposes, no patentable weight will be given to the terms "substantial" and "substantially". Correction is required.

11. Claim 100 is indefinite in the recitation of "wherein the factor is a polymerase enhancing factor" for the following reasons. Claim 96, from which claim 100 depends, is directed to a composition which comprises in part a factor that inhibits the incorporation of undesired nucleotides or analogs thereof into a DNA polymer. The specification defines the term "polymerase enhancing activity" as the ability to increase the rate, fidelity, and/or yield of a nucleic acid polymerization reaction mediated by a nucleic acid polymerase, or to expand or alter the range of conditions under which such reaction does or may

proceed. Thus, based on this definition, a polymerase enhancing factor is not limited to a factor that substantially inhibits incorporation of undesired nucleotides into a DNA polymer. The term "polymerase enhancing factor" is broader in scope. Thus, it is unclear as to how the limitation recited in claim 100 further limits claim 96. For examination purposes, no patentable weight will be given to the term. As such, claim 100 will be considered a duplicate of claim 96. Correction is required.

12. Claim 112 is indefinite in the recitation of "wherein at least two of (a), (b), and (c) are combined" for the following reasons. As written, it is unclear if the intended limitation refers to (1) the components are combined prior to use (i.e., one or two vials would comprise (a), (b), and (c) instead of individual vials for (a), (b) and (c)), or (2) the components are combined during use. For examination purposes, it will be assumed that the claim reads of "wherein at least two of (a), (b), and (c) are combined prior to use". Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 96-107 and 110-112 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 96-107 are directed to a composition comprising (1) an enzyme having 3' to 5' exonuclease activity, (2) a DNA polymerase having less 3' to 5' exonuclease activity than the enzyme of (1), and (3) a factor which inhibits the incorporation of undesired nucleotides into a DNA polymer.

Claims 110-112 are directed to a kit for amplifying, synthesizing, or mutagenizing nucleic acids, wherein said kit comprises the composition described above, and wherein the ingredients in the composition are either separate or combined prior to use. See Claim Rejections under 35 USC 112, second paragraph for claim interpretation.

As stated in MPEP 2163, "when filing an amendment an applicant should show support in the original disclosure for new or amended claims". Applicants have indicated in pages 5-6 of the response filed on 3/24/2005 that support for new claims 96-112 is found in specific sections of the specification and the claims as originally filed. The Examiner has reviewed those sections/claims referred to by Applicants in the response, and while there is support for a composition comprising Taq DNA polymerase, Pfu DNA polymerase and a *P. furiosus* protein complex having polymerase enhancing activity which appears to have a molecular weight of 300 KDa, wherein the protein complex comprises two components having a molecular weight of 45 and 50 KDa, and wherein one of the components appears to have dUTPase activity (page 68, lines 13-25), the Examiner has been unable to find support for a composition comprising (1) any enzyme having 3' to 5' exonuclease activity, (2) any DNA polymerase having less 3' to 5' exonuclease activity than the enzyme of (1), and (3) any factor which inhibits the incorporation of undesired nucleotides into a DNA polymer, or a kit comprising said composition. Also, it is noted that the Examiner has not been able to find support for a kit as claimed wherein at least two of the components are combined prior to use. The composition for which the Examiner has found support does not provide support for the entire genus of compositions/kits encompassed by the claims. There is no indication in the specification suggesting that one of the preferred embodiments of the invention is a composition/kit comprising the recited components. A statement in the specification providing support for a species, does not inherently provide support for an entire genus. Instead, the specification must show an indication that a genus is intended to be a preferred embodiment of the invention. As stated in MPEP 2163, "new claims which introduce elements or limitations which are not supported by the as-filed

disclosure violate the written description requirement. See, e.g., In re Lukach, 442 F.2d 967, 169 USPQ 795 (CCPA 1971) (subgenus range was not supported by generic disclosure and specific example within the subgenus range); In re Smith, 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972) (a subgenus is not necessarily described by a genus encompassing it and a species upon which it reads)". There is no indication that the genus recited in claims 96-107 and 110-112 was within the scope of the invention as conceived by Applicants at the time the application was filed. Accordingly, Applicants are required to cancel the new matter in response to this Office Action.

15. Claims 96-107 and 110-112 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 96-107 are directed to a composition comprising (1) a genus of enzyme having 3' to 5' exonuclease activity, (2) a genus of DNA polymerases having less 3' to 5' exonuclease activity than the enzymes of (1), and (3) a genus of factors which inhibits the incorporation of undesired nucleotides into a DNA polymer. Claims 110-112 are directed to a kit for amplifying, synthesizing, or mutagenizing nucleic acids, wherein said kit comprises the composition described above, and wherein (1) the ingredients in the composition are stored separate prior to use or (2) at least two of the ingredients are stored together prior to use. See Claim Rejections under 35 USC 112, second paragraph for claim interpretation.

In *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1938, the Court of Appeals for the Federal Circuit has held that "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials". As

indicated in MPEP § 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

In the instant case, the claims encompass genera of enzymes and factors lacking a structural limitation. While the specification and/or the art disclose the structure of a few enzymes having/lacking 3' to 5' exonuclease activity, and the specification discloses a single species of the genus of factors recited, it provides no information as to the structural elements required in (1) any enzyme that has 3' to 5' exonuclease activity, (2) any DNA polymerase which lacks 3' to 5' exonuclease activity, (3) any factor such that it inhibits the incorporation of undesired nucleotides in a DNA polymer, (4) any dUTPase or any thermostable dUTPase, or (5) any thermostable proofreading DNA polymerase. The specification fails to describe any additional species by any relevant, identifying characteristics or properties other than by functionality. Moreover, there is no disclosure of a correlation between the structure of those species disclosed in the specification and/or known in the art and the functions recited in the claims.

The claims encompass an extremely large genus of enzymes and factors which are structurally unrelated. A sufficient written description of a genus of enzymes may be achieved by a recitation of a representative number of enzymes defined by their amino acid sequence or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. However, in the instant case, there is no structural feature which is representative of all the members of

the genera of enzymes/factors recited. While one could argue that the structures of those enzymes/proteins disclosed in the art and/or the specification are representative of the genera of enzymes/factors recited such that the recited genera is adequately described by the disclosure/prior art, it is noted that the art teaches several examples of how even small variations in structure can lead to changes in function. For example, Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches that one conservative amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Therefore, since minor structural variations may result in different functions, and no additional information correlating structure with the recited activities has been provided, one cannot reasonably conclude that the structures disclosed are representative of all the species recited in the claims.

Due to the fact that the specification only discloses a few species of the genus of enzymes recited and a single species of the genus of factors required by the claims, as well as the lack of description of any additional species by any relevant, identifying characteristics or properties, one of skill in the art would not recognize from the disclosure that Applicant was in possession of the claimed invention.

16. Claims 96-107 and 110-112 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition and a kit comprising (1) Taq DNA polymerase, (2) Pfu DNA polymerase, and (3) a *P. furiosus* polymerase enhancing factor comprising SEQ ID NO: 71, does not reasonably provide enablement for a composition or a kit comprising (1) any enzyme having 3' to 5' exonuclease activity, (2) any DNA polymerase having less 3' to 5' exonuclease activity than the enzyme of (1), and (3) any factor which inhibits the incorporation of undesired nucleotides into a DNA polymer. The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2nd 1400 (Fed. Cir. 1988)) as follows: (1) quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence and absence of working examples, (4) the nature of the invention, (5) the state of prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breath of the claims. The factors which have lead the Examiner to conclude that the specification fails to teach how to make and/or use the claimed invention without undue experimentation, are addressed in detail below.

The breath of the claims. Claims 96-107 and 110-112 are so broad as to encompass (1) a composition comprising (i) any enzyme having 3' to 5' exonuclease activity, (ii) any DNA polymerase having less 3' to 5' exonuclease activity than the enzyme of (i), and (iii) any factor which inhibits the incorporation of undesired nucleotides into a DNA polymer, and (2) a kit comprising the composition of (1) wherein the components of said composition are either stored separately prior to use or at least two of them are stored together prior to use. See Claim Rejections under 35 USC 112, second paragraph for claim interpretation.

The enablement provided is not commensurate in scope with the claims due to the extremely large number of enzymes, DNA polymerases, and factors of unknown structure recited in the claims. Since there is no structural limitation associated with the recited genera of enzymes and factors, and the specification provides no correlation between the structures disclosed and the recited activities, the genera encompass enzymes and factors which the skilled artisan would not know how to make and/or use as their structure is unknown. In the instant case, the specification discloses a composition and a kit comprising (1) Taq DNA polymerase, (2) Pfu DNA polymerase, and (3) a *P. furiosus* polymerase enhancing factor comprising SEQ ID NO: 71.

The amount of direction or guidance presented and the existence of working examples. The specification discloses a composition comprising (1) Taq DNA polymerase, (2) Pfu DNA polymerase, and (3) a *P. furiosus* polymerase enhancing factor comprising SEQ ID NO: 71 as a working example. However, the specification fails to provide any clue as to the structural elements required in any enzyme having 3' to 5' exonuclease activity, any DNA polymerase lacking 3' to 5' exonuclease activity, or any factor which inhibits incorporation of undesired nucleotides into a DNA polymer. No correlation between structure and the recited activities has been presented. There is no information or guidance as to which amino acid residues in the polypeptide of SEQ ID NO:71 are required in any protein such that it would inhibit incorporation of undesired nucleotides into a DNA polymer.

The state of prior art, the relative skill of those in the art, and the predictability or unpredictability of the art. The amino acid sequence of a protein determines the structural and functional properties of that protein. In the instant case, neither the specification nor the art provide a correlation between structure and activity such that one of skill in the art can envision the structure of any enzyme having 3' to 5' exonuclease activity, any DNA polymerase lacking 3' to 5' exonuclease activity, or any factor which inhibits incorporation of undesired nucleotides into a DNA polymer.
In addition, the art does not provide any teaching or guidance as to (1) which are the structural elements in those enzymes known in the art having 3' to 5' exonuclease activity required in any enzyme having 3' to 5' exonuclease activity, (2) which are the structural elements in those DNA polymerases lacking 3' to 5' exonuclease activity which are required in any DNA polymerase lacking 3' to 5' exonuclease activity, (3) which are the structural elements in the *P. furiosus* protein complex disclosed in the specification which are required in any protein such that it would inhibit incorporation of undesired nucleotides in a DNA polymer, and (4) the general tolerance of (i) enzymes having 3'-5' exonuclease activity, (ii) DNA polymerases lacking 3'-5' exonuclease activity, and (iii) the *P. furiosus* protein complex disclosed in the specification to structural modifications, and the extent of such tolerance. The art clearly teaches that

variations in a protein's amino acid sequence to obtain the desired activity without any guidance/knowledge as to which amino acids in a protein are required for that activity is highly unpredictable. At the time of the invention there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity. For example, Branden et al. (Introduction to Protein Structure, Garland Publishing Inc., New York, page 247, 1991) teach that (1) protein engineers are frequently surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes, (2) the often surprising results obtained by experiments where single mutations are made reveal how little is known about the rules of protein stability, and (3) the difficulties in designing *de novo* stable proteins with specific functions. The teachings of Branden et al. are further supported by the teachings of Witkowski et al. (Biochemistry 38:11643-11650, 1999) and Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) already discussed above, where it is shown that even small amino acid variations result in enzymatic activity changes.

The quantity of experimentation required to practice the claimed invention based on the teachings of the specification. While methods of generating or isolating variants of a polypeptide were known in the art at the time of the invention, it was not routine in the art to screen by a trial and error process for all enzymes having 3' to 5' exonuclease activity, all DNA polymerases lacking 3' to 5' exonuclease activity, or all factors which inhibit incorporation of undesired nucleotides in a DNA polymer. In the absence of (1) a rational and predictable scheme for modifying amino acids in those enzymes/proteins known in the art (or disclosed in the specification) such that the resulting variant would display the recited activities, and/or (2) a correlation between structure and the recited activities, one of skill in the art would have to test an essentially infinite number of polypeptides to determine which ones display the recited activity. Since the claims also encompass factors which are not proteins, it would also require undue experimentation to determine the actual nature of those factors recited in the claims.

While enzymatic assays are well known in the art, and the skilled artisan can produce variants of those enzymes known in the art or disclosed in the specification, the amount of experimentation required is not routine due to the fact that the number of species encompassed by the claims is extremely large. While current screening techniques in the art would allow for testing a limited number of species, testing the virtually infinite number of proteins/factors encompassed by the claims without any guidance/suggestion as to which species should be tested would not be possible. Therefore, while enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, as is the case herein, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed so that a reasonable number of species can be selected for testing. In view of the fact that such guidance has not been provided in the instant specification, it would require undue experimentation to enable the full scope of the claims.

Therefore, taking into consideration the extremely broad scope of the claims, the lack of guidance, the amount of information provided, the lack of knowledge about a correlation between structure and function, the high degree of unpredictability of the prior art in regard to structural variations and their effect on function, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to practice the claimed invention. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 USC § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

18. Claims 96, 100, 102-106, 110-112 are rejected under 35 U.S.C. 102(b) as being anticipated by Sorge et al. (U.S. Patent No. 5556772 issued on 9/17/1996; cited in the IDS).

Sorge et al. teach compositions and kits comprising Taq (*T. aquaticus)* DNA polymerase (lacks 3'-5' exonuclease activity) and Pfu *(P. furiosus)* DNA polymerase (has 3'-5' exonuclease activity). The Taq DNA polymerase and Pfu DNA polymerase are in a buffered solution comprising $MgCl_2$, which Sorge et al. describe as a compound which increases the fidelity of Taq DNA polymerase (column 2, lines 8-24; Table 2, last column, 2.0 mM $MgCl_2$ and 237.5 μM dNTP; column 7, lines 49-62). Sorge et al. also teach kits comprising the composition wherein the kits comprise the reagents mixed together or in separate form, and also comprises reagents used in PCR (column 5, lines 7-19; column 2, lines 45-55).

Claims 96, 100, 102-106 and 110-112 are directed in part to (1) a composition comprising (i) a *T. aquaticus* DNA polymerase, (ii) a *P. furiosus* DNA polymerase, (iii) any factor which inhibits the incorporation of undesired nucleotides into a DNA polymer, and (iv) a PCR additive or a protein, and (2) a kit comprising the composition of (1) wherein the components of said composition are stored separately or together prior to use. See Claim Rejections under 35 USC 112, second paragraph for claim interpretation. A compound which increases fidelity of a DNA polymerase would be considered a compound which inhibits the incorporation of undesired nucleotides into a DNA polymer since increasing fidelity requires a reduction in the incorporation of undesired nucleotides into a DNA polymer. Therefore, the compositions and kits of Sorge et al. comprising Taq DNA polymerase, Pfu DNA polymerase, $MgCl_2$ and reagents used in PCR anticipate the instant claims as written.

Claim Rejections - 35 USC § 103

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill

in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

21. Claim 107 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sorge et al. (U.S. Patent No. 5556772 issued on 9/17/1996; cited in the IDS) in view of Huang et al. (DNA Cell Biol. 15(7):589-594, 1996). The teachings of Sorge et al. have been described above. Sorge et al. does not teach a composition further comprising an additional factor which inhibits the incorporation of undesired nucleotides into a DNA polymer. Huang et al. (Abstract; page 590, left column, lines 15-22) teach compositions comprising gene 32 protein (gp32) and (1) Deep Vent DNA polymerases (from *Pyrococcus* sp. strain GB-D) having 3'-5' exonuclease activity (wild-type), or (2) Deep Vent DNA polymerases lacking 3'-5' exonuclease activity (exo- mutant). Huang et al. disclose that gp32 increases fidelity of the wild type Deep Vent DNA polymerase by 30% (page 591, right column, lines 43-49; Table 1, error rate for first entry; Abstract). Huang et al. does not teach the addition of another factor which inhibits the incorporation of undesired nucleotides into a DNA polymer.

Claim 107 is directed to the composition of claim 96 as described above, wherein the composition further comprises a second factor which inhibits the incorporation of undesired nucleotides into a DNA polymer. See Claim Rejections under 35 USC 112, second paragraph for claim interpretation.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to add gp32 to the composition of Sorge et al. A person of ordinary skill in the art is motivated to add

gp32, as taught by Huang, in the composition of Sorge et al. for the benefit of increasing fidelity in DNA amplification. One of ordinary skill in the art has a reasonable expectation of success at adding gp32 to the composition of Sorge et al. and observing enhancement in fidelity in view of the teachings of Huang et al. which disclose that the error rate of a wild-type *Pyrococcus* DNA polymerase (Deep Vent) is reduced almost 30% by gp32. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

Double Patenting

22. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

23. Claims 96-98, 100, 102-107, 110-112 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of copending application No. 11/067304 (common inventor Holly Hogrefe). An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re*

Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

Claim 1 of copending application No. 11/067304 is directed to a composition comprising (1) a thermostable non-proofreading DNA polymerase, (2) a thermostable proofreading DNA polymerase, and (c) a factor that substantially inhibits the incorporation of undesired nucleotides (or analogs thereof) into a DNA polymer. The specification of copending application No. 11/067304 equates the term "3' to 5" exonuclease activity" with proofreading (page 4, line 7). Claims 96, 100, and 102 are directed in part to a composition comprising (1) a thermostable enzyme having 3'-5' exonuclease activity, (2) a DNA polymerase having less 3'-5' exonuclease activity than the enzyme of (1), and a factor which inhibits the incorporation of undesired nucleotides or analogs thereof into a DNA polymer. Thus, claim 1 of copending application No. 11/067304 anticipates claims 96, 100 and 102 as written.

Claims 97-98, 103-107, 110-112 of the instant application are directed in part to (1) the composition of claim 96 wherein the factor is a thermostable dUTPase, the DNA polymerases are from *P. furiosus* and *T. aquaticus*, and the composition further comprises an additional factor which inhibits incorporation of undesired nucleotides in a DNA polymer, and at least one component selected from a PCR additive and a protein, and (2) kits comprising the composition of (1) wherein the ingredients in the composition are stored separately or wherein at least two of the ingredients are combined prior to use. The specification of copending application No. 11/067304 discloses as preferred embodiments (1) Taq (*T. aquaticus*) DNA polymerase as the non-proofreading DNA polymerase, (2) Pfu (*P. furiosus*) DNA polymerase as the proofreading DNA polymerase, (page 9, lines 19-20), (3) a thermostable dUTPase (page 20, line 20-page 21, line 1), (4) kits comprising the DNA polymerases and the factor that inhibits the incorporation of undesired nucleotides into a DNA polymer, wherein the components are in separate containers prior to use or at least two of the components are combined prior to use (page 10, line 10-page 11, line 2), (5) compositions comprising the DNA polymerases, a dUTPase as well as PCR

additives/proteins (page 8, line 15-page 9, line 5), and (6) compositions which further comprise additional factors which inhibit the incorporation of undesired nucleotides into a DNA polymer (page 25, lines 12-16). In view of the specific embodiments described in the specification of copending application No. 11/067304, the invention of claims 97-98, 103-107, 110-112 of the instant application is deemed an obvious variation of the invention of claim 1 of copending application No. 11/067304.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

24. Claims 96-100, 102-107, 110-112 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 35 of copending application No. 10/702400 (common assignee Stratagene).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

Claims 96-100, 102-107 and 110-112 of the instant application are directed in part to (1) a composition comprising (i) Taq DNA polymerase, (ii) Pfu DNA polymerase, (iii) *a P. furiosus* dUTPase, (iv) a PCR additive/protein, and (v) an additional factor which inhibits incorporation of undesired nucleotides in a DNA polymer, and (2) kits comprising the composition of (1) wherein the components are stored separately or combined prior to use.

Claim 35 of copending application No. 10/702400 is directed to a blend of polymerases wherein said blend comprises non-chimeric Pfu DNA polymerase, non-chimeric Taq DNA polymerase, and at least one chimeric DNA polymerase. The specification clearly discloses the addition of a Pfu (*P. furiosus*) dUTPase (thermostable) to the blend as well as other PCR additives (page 51, lines 22-28; page 57, line 9-page 58, line 18) as a preferred embodiment. This is also evidenced by claim 42 of copending application No. 10/702400. The specification further discloses kits comprising the blends, wherein the components of the blend are placed in separate containers prior to use, or wherein the components of the blend are combined prior to use (page 63, line 16-page 64,line 9) as a preferred embodiment. Kits as preferred embodiments are also evidenced by claims 43-44 of copending application No. 10/702400. The specification also discloses the addition of other PCR additives such as Mg^{2+} to increase fidelity in DNA amplification (page 55, lines 4-8). In view of the specific embodiments described in the specification of copending application No. 10/702400, the invention of claims 96-100, 102-107 and 110-112 of the instant application is deemed an obvious variation of the invention of claim 35 of copending application No. 10/702400.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

25. No claim is in condition for allowance.

26. In June 2004, the USPTO ceased mailing paper copies of cited U.S. patents and U.S. patent application publications with all Office actions. See "USPTO to Provide Electronic Access to Cited U.S. Patent References with Office Actions and Cease Supplying Paper Copies," 1282 O.G. 109 (May 18, 2004). Foreign patent documents and non-patent literature will continue to be provided to the applicant on paper.

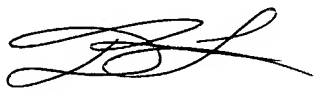
All U.S. patents and U.S. patent application publications are available free of charge from the USPTO web site (www.uspto.gov/patft/index.html), for a fee from the Office of Public Records (http://ebiz1.uspto.gov/oems25p/index.html), and from commercial sources. Copies are also available at the Patent and Trademark Depository Libraries (PTDLs). A list of the PTDLs may be found on the

USPTO web site (www.uspto.gov/web/offices/ac/ido/ptdl/ptdlib_1.html). Additionally, a new feature in the Office's Private Patent Application Information Retrieval system (PAIR), E-Patent Reference, is available for downloading and printing of U.S. patents and U.S. patent application publications cited in U.S. Office Actions.

27. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

28. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.



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DR
May 26, 2006